different subcellular compartments. Upon exposure to soluble host factors, microbial products, or microbes, the PMN phenotype rapidly transforms; first ingesting the microbe and thereby sequestering it in the phagosome, and then recruiting and activating a variety of responses targeted to kill and degrade the trapped microbe. This presentation aims to discuss some of the mechanisms underlying specific features of the PMN response within the context of innate immune response to and resolution of infection. Concomitant with PMN activation, membrane-bound granule compartments fuse with the nascent phagosome, thereby delivering enzymes as well as antimicrobial peptides directly to the microbe. Concurrently, the NADPH oxidase is assembled and activated at the phagosome membrane, generating reactive oxygen species that directly and indirectly contribute to microbial killing and degradation. Collectively, these orchestrated responses of the PMN create an intraphagosomal environment inhospitable to the phagocytosed microbe. The mechanisms underlying the generation and antimicrobial action of several bioactive species will be highlighted, as will the specific synergies between soluble circulating proteins and PMN responses that collaborate to eradicate invading microbes. PMN contribute to host defense in ways other than those directly associated with phagocytosis, as they release IL-8 and other chemokines to recruit additional immune cells to the fray and to modulate the antimicrobial activities of resident cells at the site of infection. Lastly, PMN direct biochemical and cellular events that contribute to the subsequent resolution of the inflammatory response, an essential step in returning to a homeostatic, resting state.

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Community-Acquired MRSA: What in the World is Going on? (invited)

52.001

The Origin and Evolution of MRSA

B. Kreiswirth

Public Health Research Institute, New Jersey, NJ, USA

Since the identification of the first methicillin resistant *S. aureus* (MRSA) isolate in 1961, there is extensive literature on its successful spread in the nosocomial setting, its incremental rise in antibiotic resistance and more recently, its emergence as a community associated pathogen spreading in otherwise healthy populations. Extensive genotyping of *S. aureus*, including genome sequencing of six MRSA strains, and determining the organization of the staphylococcal chromosomal cassettes that harbor the methicillin resistance gene, mecA, have identified six major pandemic clones that have spread along epidemic waves, consistent with the historic outbreaks caused by penicillin resistant in the 1950s. The current epidemic strain, commonly referred to as USA300, has aggressively spread across the United States causing an inordinate number of skin and soft tissue infections in diverse healthy populations ranging from children to senior citizens. Comparative genomic sequencing of the molecular scars of an epidemic strain that is rapidly changing. This lecture will discuss *S. aureus* epidemic waves and the current emergence of community associated MRSA.

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52.002

Evasion of Innate Host Defense by *Staphylococcus aureus*

F. DeLeo

Laboratory of Human Bacterial Pathogenesis, NIAID, Hamilton, MT, USA

Human polymorphonuclear leukocytes (PMNs or neutrophils) are essential to the innate immune response against invading microorganisms. Although most bacteria are killed readily by PMNs, pathogens such as *Staphylococcus aureus* have evolved multiple mechanisms to circumvent destruction by neutrophils and thereby cause human infections. Notably, prominent community-associated methicillin-resistant *S. aureus* (CA-MRSA) strains have enhanced ability to evade killing by human PMNs and rapidly destroy these critical innate immune cells. CA-MRSA immune evasion is multifactorial and includes resistance to antimicrobial peptides, detoxification of neutrophil reactive oxygen species, production of cytolytic molecules, and reprogramming of normal neutrophil apoptosis or turnover. Collectively, the current data indicate enhanced CA-MRSA virulence is linked to evasion of killing by neutrophils, which likely underlies (at least in part) the ability of prominent CA-MRSA strains to cause disease in individuals without known risk factors for infection.

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52.003

Microbial Pathogenesis of Community-Acquired MRSA Infections

T.J. Foster

Trinity College Dublin, Dublin, Ireland

Staphylococcus aureus is a commensal of the anterior nares. It permanently colonizes the moist squamous epithelium of about 20% of the population and intermittently colonizes another 60%. Several different bacterial surface proteins promote adhesion to desquamated nasal epithelial cells. Clumping factor B and iron-regulated surface determinant IsdA have been shown to stimulate efficient colonization of the nares of rodents, and in the case of ClfB, humans. ClfB binds to host cytokeratin 10 which is exposed on the surface of desquamated epithelial cells. When *S.aureus* breeches the skin it can cause both localized and invasive infections. The bacterium can express a plethora of surface-located and secreted molecules that promote infection. Surface proteins promote adhesion of bacteria to host cells and tissues. Surface polysaccharides and proteins help the bacterium to evade innate immune responses by inhibiting phagocytosis by neutrophils. The organism secretes proteins that can intefere with neutrophil migration and with complement

fixation which reduces the level of opsonins. It can co-opt host proteases to destroy opsonins on the bacterial surface. Several different pore-forming toxins are secreted, some of which destroy neutrophils (alpha-toxin and Panton Valentine Leucocidin). If taken up by phagocytic cells *S.aureus* can resist intracellular killing mechanisms such as lysozyme, free oxygen radicals and antimicrobial peptides. *S.aureus* can secrete proteins called superantigens which trigger the activation of T cells in a manner that lacks the specificity of antigen presentation. This causes depletion of immune cells and the failure to mount a robust response with immunological memory and may help explain the recurrent nature of infections. This presentation will review current knowledge of the phenomena of colopnization and disease pathogenesis gathered from studies with many strains of *S.aureus*. Reference will be made to CA-MRSA where appropriate.

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52.004

Clinical Aspects of the Community-Acquired MRSA Epidemic

H. Chambers

University of California San Francisco, San Francisco, CA, USA

Prevalence of methicillin-resistant *Staphylococcus aureus*(MRSA) in the community is high and rising both in the United States and in other countries. USA300 and USA400, are the predominant community-associated MRSA (CA-MRSA) clones circulating in US communities. Enhanced transmissibility and fitness, and hypervirulence characterize and probably drive emergence of MRSA in the community. The burden of disease caused by MRSA in the community exceeds that occurring in hospitals. In addition, community strains of MRSA are now a major cause of hospital-onset infections. Identification of multiple-drug resistant variants of community MRSA strains is of particular concern. Emergence of CA-MRSA has a profound impact on choice of therapy for treatment of all staphylococcal infections. For those treated as out-patients, clinicians must increasingly rely on second line agents, often in the absence of good data supporting their effectiveness. For hospitalized patients, an inevitable consequence is even greater use of vancomycin. This will increase the already considerable pressure for selection of vancomycin non-susceptible strains. Use of vancomycin will likely be accompanied by a higher rate of treatment failure. Several alternative drugs are available for treatment of MRSA, but none of these has yet been shown to be superior to vancomycin. The search for new approaches to prevention and treatment of staphylococcal infections has never been more important.

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Partnering in R&D to Develop New Drugs for the Most Neglected Diseases (invited)

53.001

Overview Abstract for the Symposium: Partnering in R&D to develop new drugs for the most neglected diseases

Description: Tropical diseases such as chloroquine-resistant malaria, leishmaniasis, lymphatic filariasis, Chagas disease, human African trypanosomiasis (HAT), dengue fever, and schistosomiasis continue to cause significant morbidity and mortality worldwide. With few new treatments that tend to be unaffordable and poorly adapted to the field, physicians are forced to use old tropical medicines that are increasingly ineffective due to inevitable drug resistance. Together with tuberculosis and HIV/AIDS, these disabling and/or life-threatening diseases represent an enduring unmet medical need and are collectively called ''neglected diseases''.

Of the 1,556 new drugs approved between 1975 and 2004, only 21 (1.3%) were specifically developed for tropical diseases and tuberculosis, even though these diseases account for 11.4% of the global disease burden. With exponential progress made in the basic knowledge of many infectious diseases, it is ironic that the drugs currently used to treat kinetoplastid diseases were discovered decades ago. With few exceptions, the wealth of basic research knowledge of these parasites is not being translated into practical applications.

Although the R&D landscape has significantly changed for neglected diseases since 2000, the need remains for new field-adapted drugs for the kinetoplastid diseases. Founded in 2003 to address the needs of patients with these most neglected diseases, DNDi (Drugs for Neglected Diseases initiative) is a collaborative, patients' needs-driven, not-for-profit drug R&D organization that is currently developing new treatments against sleeping sickness (human African trypanosomiasis, HAT), visceral leishmaniasis (VL), Chagas disease, and malaria.

The only way to improve control is to develop innovative new drugs and diagnostics and ensure they are available to patients. This symposium aims to review the opportunities and challenges ahead in the different phases of research and development of new drugs for the most neglected diseases.

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Extensively Drug-Resistant TB: New Name or New Problem (invited)

54.001

The Epidemiology of XDR TB in KwaZulu Natal South Africa: A New name or a New Problem

R. Rustomjee*, A. Pym

Medical Research Council, Durban, South Africa

Introduction: The description of the AIDS-related ''Tugela Ferry'' Outbreak (TFO) of XDR TB in KwaZulu Natal focused international attention on this province of South Africa as an epicenter of an XDR TB epidemic of unknown proportion. Similarly the global burden of TB drug-resistance, particularly in countries with the highest incidence of HIV and TB is